Effect of Aspirin Coadministration on the Safety of Celecoxib, Naproxen, or Ibuprofen

Reed, Grant W ; Abdallah, Mouin S ; Shao, Mingyuan ; Wolski, Kathy ; Wisniewski, Lisa ; Yeomans, Neville ; Lüscher, Thomas F ; Borer, Jeffrey S ; Graham, David Y ; Husni, M Elaine ; Solomon, Daniel H ; Libby, Peter ; Menon, Venu ; Lincoff, A Michael ; Nissen, Steven E

Abstract: BACKGROUND The safety of nonsteroidal anti-inflammatory drug (NSAID) and aspirin coadministration is uncertain. OBJECTIVES The aim of this study was to compare the safety of combining NSAIDs with low-dose aspirin. METHODS This analysis of the PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen) trial included 23,953 patients with osteoarthritis or rheumatoid arthritis at increased cardiovascular risk randomized to celecoxib, ibuprofen, or naproxen. The on-treatment population was used for this study. Outcomes included composite major adverse cardiovascular events, noncardiovascular death, gastrointestinal or renal events, and components of the composite. Cox proportional hazards models compared outcomes among NSAIDs stratified by aspirin use following propensity score adjustment. Kaplan-Meier analysis was used to compare the cumulative probability of events. RESULTS When taken without aspirin, naproxen or ibuprofen had greater risk for the primary composite endpoint compared with celecoxib (hazard ratio [HR]: 1.52; 95% confidence interval [CI]: 1.22 to 1.90, p <0.001; and HR: 1.81; 95% CI: 1.46 to 2.26; p <0.001, respectively). Compared with celecoxib, ibuprofen had more major adverse cardiovascular events ($p < 0.05$), and both ibuprofen and naproxen had more gastrointestinal ($p < 0.001$) and renal ($p < 0.05$) events. Taken with aspirin, ibuprofen had greater risk for the primary composite endpoint compared with celecoxib (HR: 1.27; 95% CI: 1.06 to 1.51; $p < 0.01$); this was not significantly higher with naproxen (HR: 1.18; 95% CI: 0.98 to 1.41; $p = 0.08$). Among patients on aspirin, major adverse cardiovascular events were similar among NSAIDs, and compared with celecoxib, ibuprofen had more gastrointestinal and renal events ($p < 0.05$), while naproxen had more gastrointestinal events ($p < 0.05$), without a difference in renal events. Similar results were seen on adjusted Kaplan-Meier analysis. CONCLUSIONS Celecoxib has a more favorable overall safety profile than naproxen or ibuprofen when taken without aspirin. Adding aspirin attenuates the safety advantage of celecoxib, although celecoxib is still associated with fewer gastrointestinal events than ibuprofen or naproxen and fewer renal events than ibuprofen. (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen or Naproxen [PRECISION]; NCT00346216).

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ABSTRACT

BACKGROUND The safety of nonsteroidal anti-inflammatory drug (NSAID) and aspirin coadministration is uncertain.

OBJECTIVES The aim of this study was to compare the safety of combining NSAIDs with low-dose aspirin.

METHODS This analysis of the PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen) trial included 23,953 patients with osteoarthritis or rheumatoid arthritis at increased cardiovascular risk randomized to celecoxib, ibuprofen, or naproxen. The on-treatment population was used for this study. Outcomes included composite major adverse cardiovascular events, noncardiovascular death, gastrointestinal or renal events, and components of the composite. Cox proportional hazards models compared outcomes among NSAIDs stratified by aspirin use following propensity score adjustment. Kaplan-Meier analysis was used to compare the cumulative probability of events.

RESULTS When taken without aspirin, naproxen or ibuprofen had greater risk for the primary composite endpoint compared with celecoxib (hazard ratio [HR]: 1.52; 95% confidence interval [CI]: 1.22 to 1.90, $p < 0.001$; and HR: 1.81; 95% CI: 1.46 to 2.26; $p < 0.001$, respectively). Compared with celecoxib, ibuprofen had more major adverse cardiovascular events ($p < 0.05$), and both ibuprofen and naproxen had more gastrointestinal ($p < 0.001$) and renal ($p < 0.05$) events. Taken with aspirin, ibuprofen had greater risk for the primary composite endpoint compared with celecoxib (HR: 1.27; 95% CI: 1.06 to 1.51; $p < 0.01$); this was not significantly higher with naproxen (HR: 1.18; 95% CI: 0.98 to 1.41; $p = 0.08$). Among patients on aspirin, major adverse cardiovascular events were similar among NSAIDs, and compared with celecoxib, ibuprofen had more gastrointestinal and renal events ($p < 0.05$), while naproxen had more gastrointestinal events ($p < 0.05$), without a difference in renal events. Similar results were seen on adjusted Kaplan-Meier analysis.

CONCLUSIONS Celecoxib has a more favorable overall safety profile than naproxen or ibuprofen when taken without aspirin. Adding aspirin attenuates the safety advantage of celecoxib, although celecoxib is still associated with fewer gastrointestinal events than ibuprofen or naproxen and fewer renal events than ibuprofen. (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen or Naproxen [PRECISION]; NCT00346216) (J Am Coll Cardiol 2018;71:1741–51) © 2018 the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

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ABBREVIATIONS AND ACRONYMS

APTC = Antiplatelet Trialists' Collaboration

CAD = coronary artery disease

CI = confidence interval

COX = cyclooxygenase

GI = gastrointestinal

HR = hazard ratio

IPTW = inverse probability of treatment weights

MACE = major adverse cardiovascular event(s)

NSAID = nonsteroidal anti-inflammatory drug

Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin is widespread. In 2010, >43 million U.S. adults were regular aspirin users, and >28 million took NSAIDs regularly (1,2). An estimated 20% to 50% of patients with osteoarthritis or rheumatoid arthritis take aspirin daily (3,4). The coadministration of NSAIDs and aspirin has raised safety concerns, because both inhibit synthesis of prostanoids in tissues in which these lipid mediators may have protective effects. Furthermore, nonselective NSAIDs may compete with aspirin for its binding site on cyclooxygenase (COX)-1 (5,6), blocking aspirin's ability to acetylate a serine residue on COX-1 necessary for platelet inhibition (6,7).

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Observational studies and meta-analyses suggest that both NSAIDs nonselective for COX-1 or COX-2 and NSAIDs selective for COX-2 have adverse effects, including cardiovascular, gastrointestinal (GI), and renal events, compared with placebo (8–13). Studies have reported conflicting results with regard to whether adding aspirin to an NSAID modifies these risks (14–19). Likewise, there have been reports of aspirin failure in patients with inflammatory disorders, particularly among patients on NSAIDs (20). The relative safety of combining aspirin and NSAIDs with various degrees of COX-1 and COX-2 inhibition is not well understood, presenting challenges to providing patient recommendations on this subject.

Accordingly, we performed a propensity score-adjusted substudy of the PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen) trial to evaluate the safety of combining aspirin (a selective COX-1 inhibitor) with celecoxib (a selective COX-2 inhibitor), naproxen (a nonselective COX-1 > COX-2 inhibitor), or ibuprofen (a nonselective COX-2 > COX-1 inhibitor).

METHODS

STUDY POPULATION. This was a post hoc analysis of the PRECISION trial. The design, rationale, and primary results of PRECISION have been previously published (3,21). Briefly, PRECISION was a multicenter, randomized controlled trial of patients with osteoarthritis or rheumatoid arthritis on long-term NSAIDs at increased cardiovascular risk that demonstrated the noninferiority of moderate-dose celecoxib (100 to 200 mg twice daily) to naproxen (375 to 500 mg twice daily) and ibuprofen (600 to 800 mg 3 times daily) with regard to cardiovascular safety. The PRECISION trial protocol pre-specified an analysis stratified by aspirin use a priori. However, the statistical methodology used to accomplish this was established post hoc.

As previously reported, in PRECISION, patients were randomized according to their primary diagnosis (osteoarthritis or rheumatoid arthritis), and stratified by low-dose aspirin (≤325 mg) use at baseline to ensure equal distribution among NSAIDs. The study protocol did not permit doses of aspirin >325 mg. All subjects were provided with once-daily esomeprazole 20 to 40 mg as a gastroprotective agent regardless of aspirin use. All patients gave informed consent before enrollment in the study.

membership on the adjudication committee in the ARIVE trial. Dr. Borer served as chair of a data and safety monitoring board for an unrelated product being developed by Pfizer; has served as a consultant, trial executive committee member, data and safety monitoring board member, or cardiac event adjudication committee member for unrelated products for Amgen, Novartis, AstraZeneca, Takeda, Biotronik, Servier, GlaxoSmithKline, Gilead, and ARMGO; and owns stock in BioMarin and ARMGO. Dr. Graham is a consultant for RedHill Biopharma regarding novel *Helicobacter pylori* therapies; has received research support from RedHill Biopharma for culture of *H. pylori*; is the principal investigator of an international study of the use of antimycobacterial therapy for Crohn's disease; and is a consultant for BioGaia in relation to probiotic therapy for *H. pylori* infection and for Takeda in relation to *H. pylori* therapies. Dr. Husni has received an institution grant to perform the PRECISION trial; has received a Sanofi Genzyme investigator grant; and has served on advisory boards for AbbVie, Bristol-Myers Squibb, Amgen, UCB, Regeneron, and Janssen. Dr. Solomon has received a research grant from Pfizer for unrelated work; and has received royalties from UpToDate for a chapter about NSAIDs. Dr. Libby has been an unpaid consultant to or has been involved in clinical trials for Amgen, AstraZeneca, Esperion Therapeutics, Ionis Pharmaceuticals, Kowa Pharmaceuticals, Merck, Novartis, Pfizer, Sanofi-Regeneron, Takeda Pharmaceuticals, and XBiotech; has served as a member of scientific advisory boards for Amgen, Corvidia Therapeutics, DalCor Pharmaceuticals, Kowa Pharmaceuticals, Olatec Therapeutics, Medimmune, and Novartis; and his laboratory has received research funding in the past 2 years from Novartis. Dr. Menon has received grant support to the institution to perform the PRECISION trial. Dr. Lincoff has received grant support to the institution to perform the PRECISION trial; is a consultant for Amgen, Novo, Nordisk, Sanofi, Abbott, Sarpeta, and Sermonix; and has received research grants to his institution from Pfizer, AstraZeneca, Esperion, AbbVie, Eli Lilly, and Roche. Dr. Nissen has received grant support to the institution to perform the PRECISION trial. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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TABLE 1 Patient Characteristics Stratified by Aspirin Use at Randomization

	No Aspirin (n = 12,935)	Aspirin (n = 11,018)	p Value
Age, yrs	61.6 ± 9.6	65.1 ± 8.8	<0.001
Female	9,063 (70.1)	6,297 (57.2)	<0.001
Race			<0.001
White	9,082 (70.2)	8,801 (79.9)	
Black	2,012 (15.6)	1,292 (11.7)	
Asian	394 (3.0)	114 (1.0)	
Unspecified/other	1,447 (11.2)	811 (7.4)	
BMI, kg/m^2	32.5 ± 7.6	32.7 ± 7.1	0.12
Arthritis diagnosis			<0.001
OA	11,409 (88.2)	10,116 (91.8)	
RA	1,523 (11.8)	902 (8.2)	
Established CAD	1,133 (8.9)	3,072 (28.1)	<0.001
Diabetes mellitus	4,138 (32.4)	4,308 (39.4)	<0.001
Hypertension	9,718 (76.1)	8,928 (81.6)	<0.001
Dyslipidemia	7,371 (57.7)	7,601 (69.5)	<0.001
Current smoker	3,151 (24.4)	1,825 (16.6)	<0.001
Current statin use	5,612 (43.4)	7,302 (66.3)	<0.001
Current DMARD use	1,097 (8.5)	651 (5.9)	<0.001
Systolic BP, mm Hg	125.3 ± 10.5	125.2 ± 10.5	0.44
Diastolic BP, mm Hg	76.1 ± 7.8	74.6 ± 8.1	<0.001
Creatinine, mg/dl	0.87 ± 0.22	0.92 ± 0.22	<0.001
C-reactive protein, mg/dl	3.0 (1.4–6.7)	2.4 (1.1–5.2)	<0.001
HAQ disability index	1.13 ± 0.61	1.08 ± 0.61	<0.001
VAS score, mm	55.4 ± 23.7	52.5 ± 23.7	<0.001

Values are mean ± SD, n (%), or median (interquartile range). Results are pooled among all nonsteroidal anti-inflammatory drugs (celecoxib, naproxen, and ibuprofen).

BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; DMARD = disease-modifying antirheumatic drug; HAQ = Health Assessment Questionnaire; OA = osteoarthritis; RA = rheumatoid arthritis; VAS = visual analogue scale.

STUDY COMPARISONS. We analyzed outcomes in PRECISION on the basis of the presence or absence of aspirin use and the specific NSAID administered, in the following comparisons: 1) aspirin versus no aspirin use among all patients (i.e., all NSAIDs pooled together); 2) aspirin versus no aspirin use among patients on celecoxib, naproxen, or ibuprofen (i.e., NSAIDs analyzed separately); 3) celecoxib, naproxen, or ibuprofen use in patients not on aspirin; and 4) celecoxib, naproxen, or ibuprofen use in patients on aspirin.

STUDY ENDPOINTS AND FOLLOW-UP. The primary endpoint for this analysis was the composite endpoint of any safety event, defined as the first occurrence of an extended major adverse cardiovascular event (MACE), noncardiovascular death, clinically significant GI event, iron-deficiency anemia of GI origin, or serious renal event. The definition of extended MACE included death due to cardiovascular causes (including hemorrhagic death), nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina or transient ischemic attack. Clinically significant GI events included acute gastric or intestinal hemorrhage, symptomatic ulcer, gastric outlet obstruction, and gastric or intestinal perforation. A serious renal event was defined as creatinine ≥2.0 mg/dl and an increase of ≥0.7 mg/dl from baseline serum creatinine, hospitalization for acute renal failure, or initiation of hemodialysis.

Secondary endpoints were individual components of the composite outcome, including extended MACE, noncardiovascular death, and GI or renal events, as well as MACE as defined by the Antiplatelet Trialists' Collaboration (APTC) criteria (death due to cardiovascular causes or hemorrhagic death, nonfatal myocardial infarction, or nonfatal stroke) (22).

Outcomes were analyzed in the modified intention-to-treat (the "on-treatment") population of patients confirmed to be taking study drug during follow-up. Patients were followed at regular intervals via office visits or telephone calls as specified in the study protocol. The protocol pre-specified a minimum follow-up duration of 18 months, with censoring of data from event-free patients through 30 days after the last dose of the study medication up to a maximum of 43 months.

STATISTICAL ANALYSIS. Baseline characteristics are presented as mean ± SD for continuous variables (as all were confirmed to be normally distributed) or count (percentage of patients) for categorical variables. There was no collinearity among covariates. For each endpoint, the raw number of events (percentage of total patients) over time is reported. Patient characteristics were stratified by the presence or absence of aspirin use at randomization, pooled in all patients (**Table 1**) as well as within each individual NSAID group (celecoxib, naproxen, and ibuprofen) (Online Table 1). Differences between aspirin and no-aspirin groups were assessed using 2-tailed Student's *t*-tests or chi-square tests.

Approximately 1.5% of patients had 1 or more missing values of baseline characteristics. To make the best use of the data, all baseline data were made complete by imputing missing values using multivariate imputation by chained equations, which was implemented with the MI procedure in SAS (SAS Institute, Cary, North Carolina). For each endpoint, 5 imputed datasets were generated. All analyses in this study other than reported in **Table 1** were performed and reported on the datasets containing imputed values but were repeated in the original nonimputed datasets to ensure consistency in results. Results

from the imputed and nonimputed datasets were very similar.

To adjust for differences between patients taking aspirin and not, propensity scores for aspirin treatment and corresponding stabilized inverse probability of treatment weights (IPTWs) were calculated using a universal binary logistic regression model including all of the baseline characteristics as covariates (23), in each of the imputed datasets for each endpoint. Improvement in the balance of baseline characteristics was assessed by evaluating a plot of the absolute standardized differences with and without IPTW (Online Figure 1). An absolute value in standardized differences of <10% for each variable served to determine adequate covariate balance (24).

Cox proportional hazards analysis was performed for each outcome using average treatment effect weighting (25), given that the treatment effect of aspirin was applied to all the study participants at baseline. The proportional hazards assumption was examined for aspirin in the overall patients and in each NSAID treatment (in the form of dummy variables) using a plot of Schoenfeld residuals; no deviation from the assumption was observed in any case. Multivariate model selection was then conducted through the stepwise selection method, incorporating normalization of stabilized IPTWs. Demographic characteristics (age, sex, race, and body mass index), presence or absence of aspirin use, and NSAID treatments were forced in, and interaction terms of covariates with time to first event were added to the model. Those with p values <0.10 were retained at each iteration. In each iteration, parameters in the Cox model were estimated using a robust variance estimator (26). The selected variables constituted the covariate set in the final Cox model, which used all the aforementioned adjustment methods for a multivariate setting. The Cox regression results from the 5 imputed datasets were then combined and reported in the form of hazard ratios (HRs) and 95% confidence interval (CIs) using the MIANALYZE procedure in SAS and were graphed in forest plots. IPTW-adjusted Kaplan-Meier curves were also created comparing outcomes among the NSAIDs in each of the aspirin and no-aspirin groups separately. Interaction testing for NSAID and aspirin use, as well as coronary artery disease (CAD) and aspirin use, were performed. A separate sensitivity analysis evaluated outcomes on the basis of the presence or absence of CAD given its possible collinearity and interaction with aspirin use. Two-sided p values <0.05 were considered to indicate statistical significance. The analyses were performed using SAS version 9.4. The forest plots were drawn using the FORESTPLOT package in R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria). The plot of absolute standardized differences was made using SigmaPlot version 11.0 (Systat, San Jose, California).

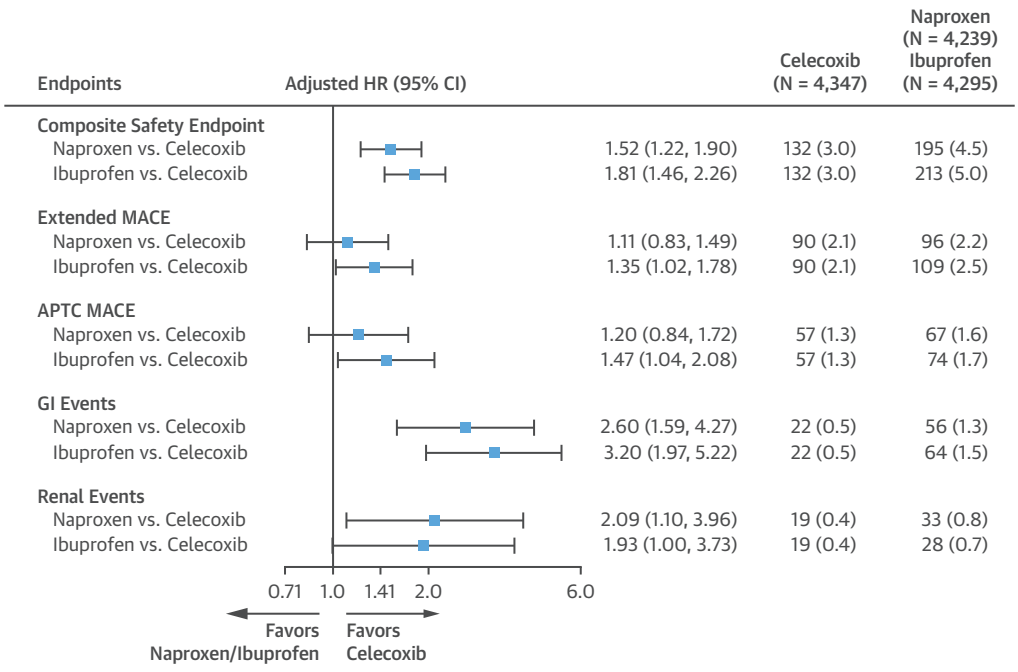
RESULTS

PATIENT CHARACTERISTICS. This study included 23,953 patients (24,222 patients were randomized in PRECISION, but 141 patients were excluded because of enrollment errors and 128 patients did not have data on aspirin use); 8,030 were assigned to celecoxib, 7,933 to naproxen, and 7,990 to ibuprofen. Aspirin was used by 11,018 patients (46.0%) at randomization; 3,683 (45.9%) were on both celecoxib plus aspirin, 3,640 (45.9%) naproxen plus aspirin, and 3,695 (46.2%) ibuprofen plus aspirin. Aspirin users were older, more likely to be male, and more likely have a history of CAD, diabetes mellitus, hypertension, dyslipidemia, and active statin use. There was a lower prevalence of smoking among aspirin users compared with nonusers (**Table 1**). The distribution of baseline characteristics was similar when evaluating each NSAID group separately (Online Table 1). The observed differences in patient characteristics were successfully balanced after propensity score weighting (Online Figure 1). Almost all patients were on proton pump inhibitors at randomization (23,816 [99.4%]).

ADDITION OF ASPIRIN TO NSAID THERAPY. There was no significant difference in the composite safety endpoint with the addition of aspirin when all NSAIDs were pooled together (adjusted HR: 1.10; 95% CI: 0.97 to 1.25; p = 0.13) (Online Figure 2). However, patients taking celecoxib plus aspirin had a higher risk for the composite safety endpoint compared with those on celecoxib alone (2.0% vs. 1.0%; adjusted HR: 1.44; 95% CI: 1.13 to 1.82; p = 0.003). This was driven by a higher rate of extended MACE with celecoxib plus aspirin compared with celecoxib alone (1.4% vs. 0.7%; adjusted HR: 1.51; 95% CI: 1.14 to 2.01; p = 0.004). There was a marginally significant interaction effect between NSAID and aspirin use (p = 0.046) on the composite safety endpoint. There were otherwise no differences in the composite safety endpoint or extended MACE with the addition of aspirin to naproxen or ibuprofen. Likewise, there were no difference in APTC-defined MACE, GI events, or renal events with the addition of aspirin for any of the NSAIDs.

OUTCOMES OF CELECOXIB, NAPROXEN, AND IBUPROFEN WITHOUT ASPIRIN. Among patients not on aspirin, naproxen or ibuprofen each associated with greater risk for the composite safety endpoint compared with patients on celecoxib (4.5% vs. 3.0%

FIGURE 1 Outcomes in Non-Aspirin Users on Naproxen or Ibuprofen Compared With Celecoxib



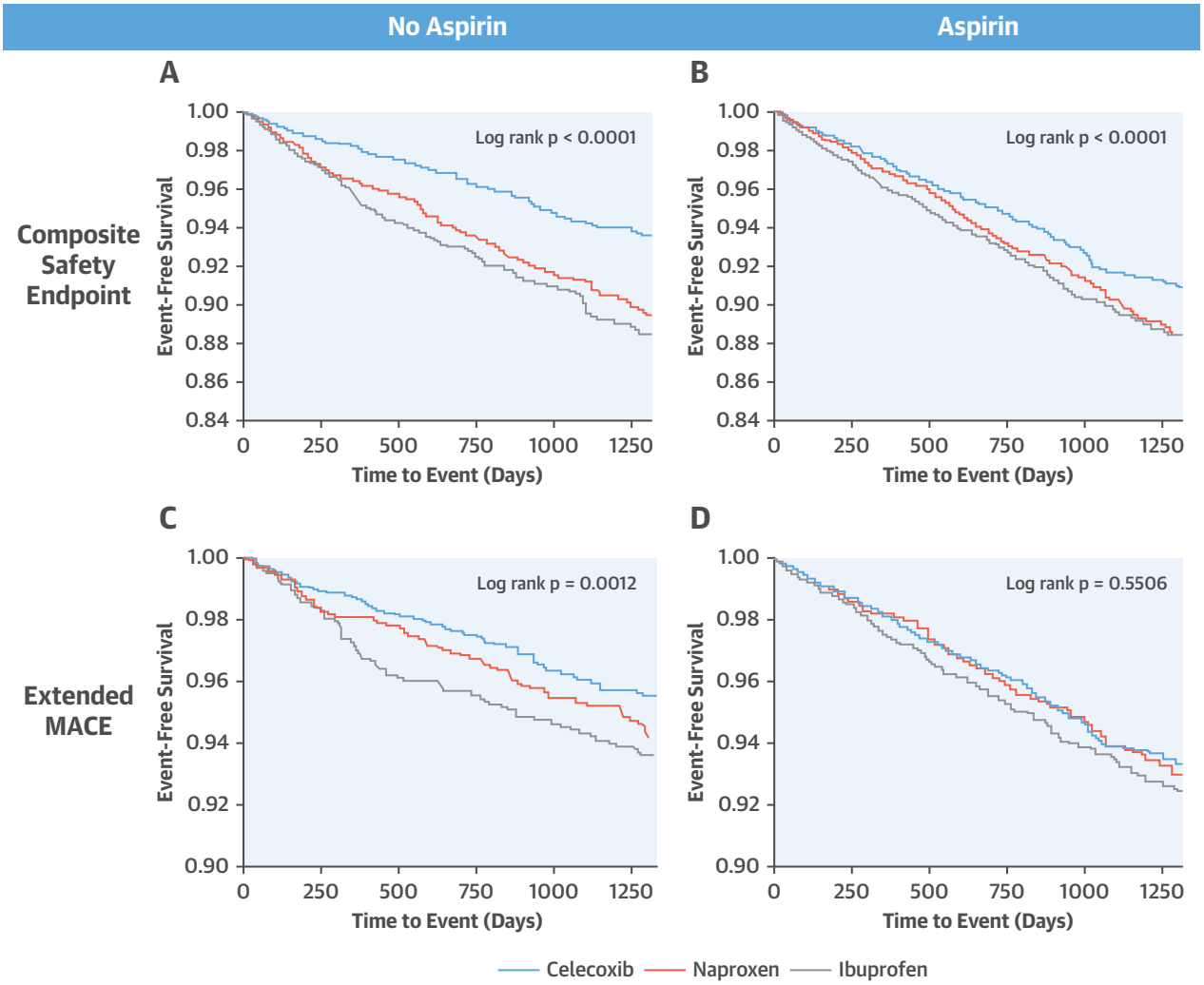
The number of events (percentage of total) is reported. APTC = Antiplatelet Trialists' Collaboration; CI = confidence interval; GI = gastrointestinal; HR = hazard ratio; MACE = major adverse cardiovascular event.

and 5.0% vs. 3.0%, respectively; naproxen vs. celecoxib adjusted HR: 1.52; 95% CI: 1.22 to 1.90; $p < 0.001$; ibuprofen vs. celecoxib HR: 1.81; 95% CI: 1.46 to 2.26; $p < 0.001$) (Figure 1). These results derived primarily from a greater risk for GI events with either naproxen compared with celecoxib (1.3% vs. 0.5%; adjusted HR: 2.60; 95% CI: 1.59 to 4.27; $p < 0.001$) and ibuprofen compared with celecoxib (1.5% vs. 0.5%; adjusted HR: 3.20; 95% CI: 1.97 to 5.22; $p < 0.001$). However, when comparing ibuprofen with celecoxib, there was also slightly higher risk for extended MACE (adjusted HR: 1.35; 95% CI: 1.02 to 1.78; $p = 0.039$) and APTC-defined MACE (adjusted HR: 1.47; 95% CI: 1.04 to 2.08; $p = 0.031$), and compared with celecoxib, naproxen was associated with a greater risk for renal events (adjusted HR: 2.09; 95% CI: 1.10 to 3.96; $p = 0.024$), while excess risk with ibuprofen was borderline significant (adjusted HR: 1.93; 95% CI: 1.00 to 3.73; $p = 0.052$).

On adjusted Kaplan-Meier analysis, the composite safety endpoint and extended MACEs occurred least frequently with celecoxib compared with naproxen or ibuprofen (Central Illustration) (log-rank $p < 0.0001$ and $p = 0.0012$, respectively). Similarly, GI events ($p < 0.0001$) and renal events ($p = 0.0005$) were least common with celecoxib compared with the other NSAIDs (Figures 2A and 2C).

OUTCOMES OF CELECOXIB, NAPROXEN, AND IBUPROFEN COMBINED WITH ASPIRIN. Patients taking ibuprofen plus aspirin had greater risk for the composite safety endpoint compared with celecoxib plus aspirin (7.1% vs. 6.0%; adjusted HR: 1.27; 95% CI: 1.06 to 1.51; $p = 0.01$) (Figure 3). However, there was no difference in extended MACE or APTC-defined MACE between NSAIDs with the addition of aspirin. The difference in the composite safety endpoint was driven by an increased risk for GI events with ibuprofen plus aspirin compared with celecoxib plus aspirin (1.4% vs. 0.9%; adjusted HR: 1.71; 95% CI: 1.10 to 2.67; $p = 0.017$), which was also observed with naproxen plus aspirin compared with celecoxib plus aspirin (1.6% vs. 0.9%; adjusted HR: 1.91; 95% CI: 1.24 to 2.94; $p = 0.003$). Likewise, the hazard of renal events was greater with ibuprofen plus aspirin compared with celecoxib plus aspirin (1.2% vs. 0.6%; adjusted HR: 2.01; 95% CI: 1.23 to 3.30; $p = 0.005$), but there was no difference with naproxen plus aspirin compared with celecoxib plus aspirin. Event rates tended to be higher for all endpoints with aspirin addition, regardless of which NSAID was used (Figures 1 and 3).

CENTRAL ILLUSTRATION **Safety of Combined Aspirin and Nonsteroidal Anti-Inflammatory Drug Use**



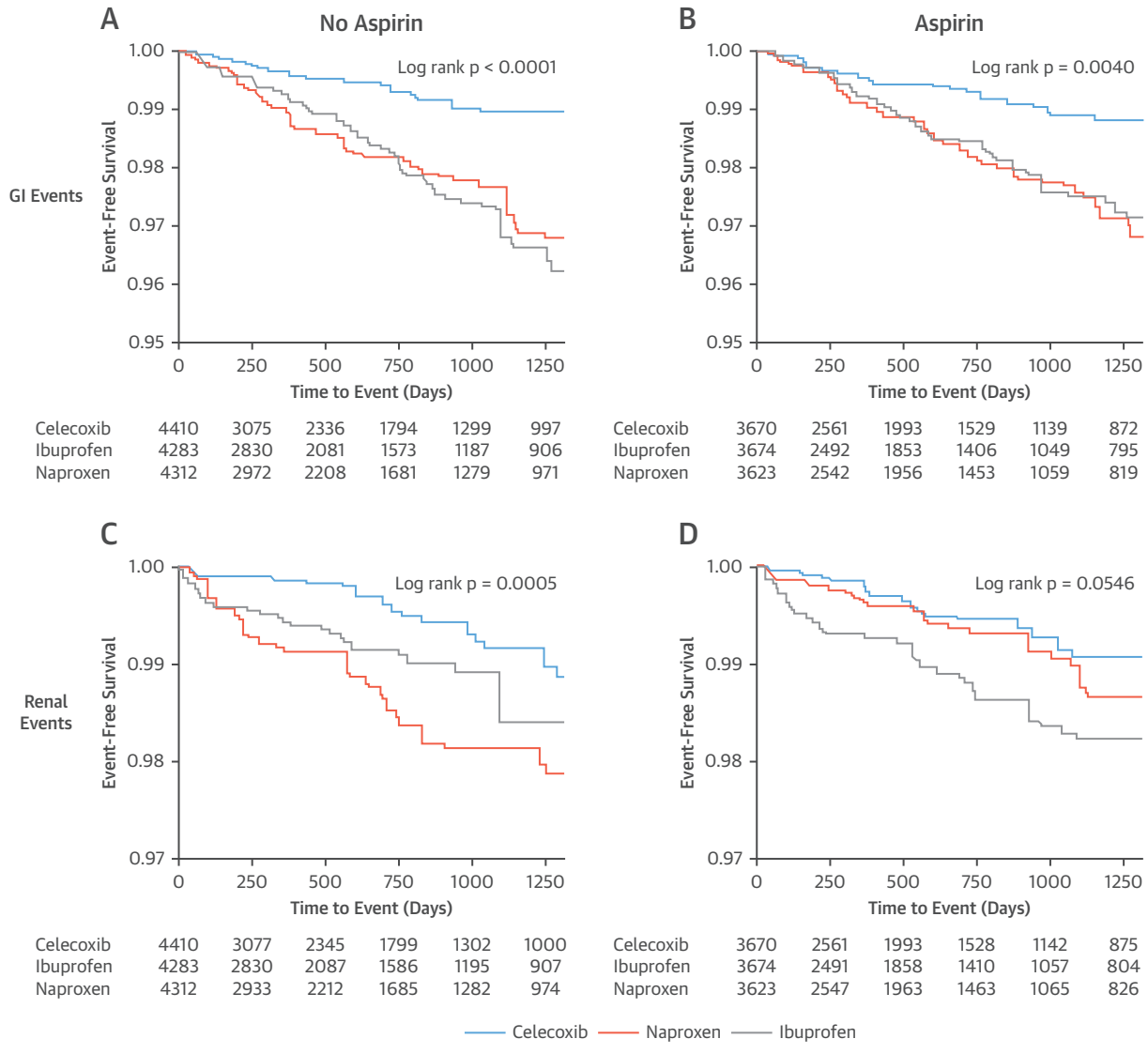
Reed, G.W. et al. J Am Coll Cardiol. 2018;71(16):1741–51.

Adjusted Kaplan-Meier curves for the composite safety endpoint and extended major adverse cardiovascular event (MACE), stratified by aspirin use. Among patients not on aspirin, celecoxib had the lowest incidence of composite safety events and extended MACE. The addition of aspirin attenuated the relative safety benefit of celecoxib.

Furthermore, adjusted Kaplan-Meier analysis demonstrated that the addition of aspirin attenuated the benefit of celecoxib compared with naproxen and ibuprofen with regard to the composite safety endpoint and extended MACE (Central Illustration). Likewise, in the presence of aspirin, there was less differentiation in renal events among NSAIDs (Figure 2D). However, GI events remained least frequent with celecoxib (log-rank p = 0.004) (Figure 2B).

CAD AND ASPIRIN COMPLIANCE SENSITIVITY ANALYSES. In a pre-specified sensitivity analysis, comparing patients with CAD with those without, the relative hazard of the composite safety endpoint was approximately the same whether aspirin was also used (adjusted HR: 2.23; 95% CI: 1.90 to 2.60; p < 0.001) or aspirin was not used (adjusted HR: 2.01; 95% CI: 1.56 to 2.59; p < 0.001), demonstrating no significant interaction between CAD and aspirin use (Online Figure 3) (interaction p = 0.35).

FIGURE 2 Adjusted Kaplan-Meier Curves for the Cumulative Incidence of Gastrointestinal and Renal Events, Stratified by Aspirin Use



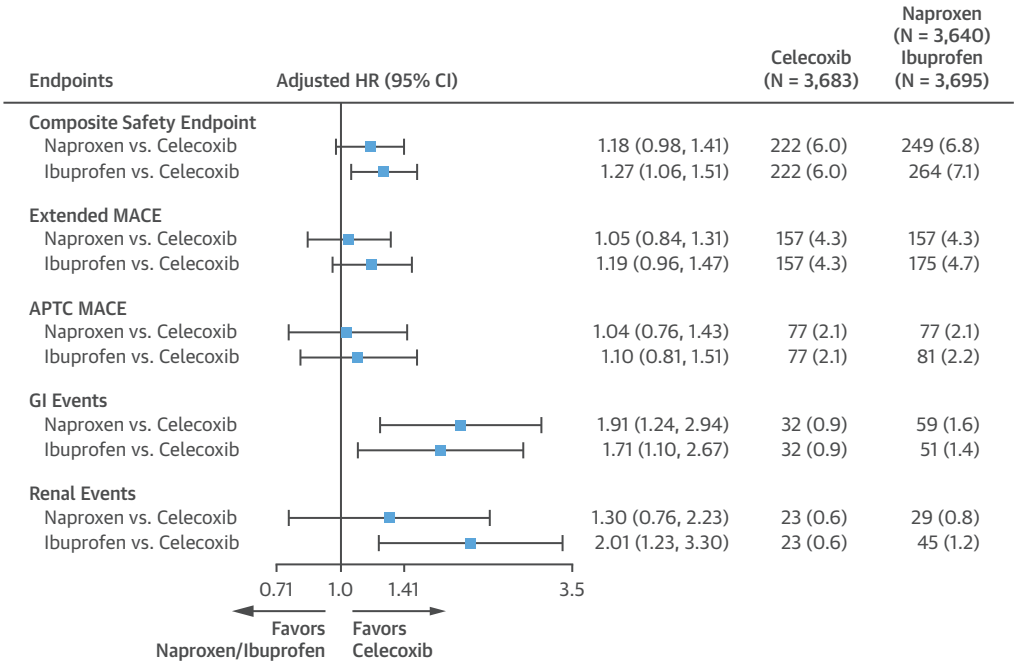
The addition of aspirin attenuated the gastrointestinal (GI) and renal safety of celecoxib, although GI events were still less frequent with celecoxib than ibuprofen or naproxen.

Only 304 patients (1.3%) discontinued aspirin after randomization, and 964 patients (4.0%) who were not on aspirin started aspirin during the study (this was equally distributed among the NSAIDs). When excluding these patients, the results for the primary endpoint were not significantly different.

DISCUSSION

This study demonstrates that the relative cardiovascular and overall safety of NSAID therapy is modified by concomitant aspirin use. Specifically, celecoxib was associated with a more favorable overall safety profile than naproxen or ibuprofen among regular NSAID users not taking aspirin. However, the addition of aspirin attenuated the relatively favorable safety profile of celecoxib, and although there was still a slight advantage of celecoxib over ibuprofen with regard to composite safety events, there were no longer differences in extended MACE or APTC-defined MACE. However, celecoxib was still associated with fewer GI events

FIGURE 3 Outcomes in Patients on Naproxen or Ibuprofen Compared With Celecoxib, With Combined Aspirin



The number of events (percentage of total) is reported. Abbreviations as in Figure 1.

than ibuprofen or naproxen and fewer renal events than ibuprofen.

The primary findings of PRECISION were reported in the intention-to-treat population, in which patients were grouped on the basis of the study drug to which they were assigned at randomization. In that analysis, events were counted regardless of whether the study drug was stopped during the study. However, in studies of drug safety, the on-treatment population can be more informative, as it considers events only while patients are actually taking the drug, and patients are censored a period of time after the study drug is stopped (30 days in the present analysis). This consideration has particular relevance to studies of patients with pain, as these patients discontinue medications frequently in favor of trying other analgesic drugs. In this case, the intention-to-treat analysis actually reflects the effects of these other medications, while effects of the study drug are better reflected in an on-treatment analysis. Indeed, in PRECISION, study drug discontinuation was more common than expected, as previously reported (see PRECISION Trial Supplemental Appendix Figure S2) (3). Furthermore, although the main findings of PRECISION did contain a subgroup analysis stratified by aspirin use, that analysis was in the intention-to-treat population. The present study was better equipped to assess the effect of aspirin on outcomes, as it was a propensity score-adjusted analysis of overall harms in the on-treatment population and thus more relevant for the reasons described.

Our findings do not support the premise that selective COX-2 inhibitors as a class increase cardiovascular risk compared with nonselective COX-1 and COX-2 inhibitors (27). On the contrary, in the primary results from the PRECISION trial, selective COX-2 inhibition with celecoxib was noninferior for cardiovascular safety to nonselective COX-2 > COX-1 inhibition with ibuprofen or COX-1 > COX-2 inhibition with naproxen in the intention-to-treat population. The present analysis of the on-treatment population is clinically more relevant with regard to safety endpoints and showed the most favorable cardiovascular safety profile in patients with the selective COX-2 inhibitor celecoxib alone. Adding COX-1 inhibition with aspirin attenuated the cardiovascular safety advantage of celecoxib and rendered the relative cardiovascular safety profiles of the NSAIDs approximately equivalent. These findings support the hypothesis and main findings of the PRECISION trial

that the increased cardiovascular risk observed with rofecoxib is not a COX-2 inhibition class effect. Furthermore, our results suggest that celecoxib has a more favorable cardiovascular safety profile than ibuprofen or naproxen among patients not on aspirin and that the cardiovascular safety profile of celecoxib is noninferior to ibuprofen or naproxen among aspirin users.

Our findings underscore the importance of appropriate patient counseling on the relative safety profile of NSAIDs when initiating therapy. Although short-term NSAID use is likely safe (28), long-term use of any NSAID has been associated with increased cardiovascular, GI, and renal risk compared with placebo in observational studies (9,29,30). However, if an NSAID is required, the relative safety of the various NSAIDs appears to be modified by concomitant aspirin use. Physicians administering any NSAID should consider the potential GI and renal hazards of using combined NSAID and aspirin therapy. It would be reasonable to consider gastric protection with an H2 blocker or proton pump inhibitor if aspirin is also used (29).

Most studies on the comparative safety of NSAIDs have not investigated a possible interaction between aspirin and NSAID use and have revealed conflicting results, likely because of their heterogeneous study designs and potential selection bias (16,17,31). A key meta-analysis of 39 trials including more than 41,000 patients prior to PRECISION suggested that the incidence of APTC-defined MACE did not differ in patients treated with celecoxib compared with nonselective NSAIDs regardless of aspirin use. However, this analysis did find a lower cardiovascular death rate with celecoxib compared with nonselective NSAIDs (relative risk: 0.43; 95% CI: 0.19 to 0.95; $p = 0.04$) (14). Other observational studies have revealed increased cardiovascular risk with ibuprofen plus aspirin compared with ibuprofen alone (15,16), while others have shown reduced risk (18) or no change at all (17,32). Our study aimed to illuminate these differences. Results of our study support the relative safety of celecoxib compared with naproxen or ibuprofen with regard to cardiovascular, GI, and renal events.

The present study is a post hoc analysis of a randomized controlled trial, and as such there were differences in patient characteristics when stratified by aspirin use (**Table 1**). This is a common issue seen in most other observational studies of NSAID and aspirin use and introduces bias that can be addressed only by a properly designed trial. A strength of the present study is the use of propensity score weighting to adjust for baseline characteristics (Online Figure 1). Our use of this technique allowed adjustment for baseline characteristics, creating a "pseudo-randomization" result, increasing the validity to our results. To the best of our knowledge, ours is the only study on this topic to use such a technique. We further incorporated multivariate adjustment into propensity score-weighted survival regression analysis, a so-called doubly robust adjustment, to reduce residual confounding as much as possible (33).

STUDY LIMITATIONS. The strengths and limitations of the PRECISION trial have been previously discussed (3). Although the analysis was pre-specified in the trial protocol, the study was not designed to detect an interaction between the study NSAIDs and aspirin. Accordingly, the present analysis should be considered hypothesis generating and needs to be confirmed by other studies. There were no comparisons of ibuprofen and naproxen in this study, though the relative safety of these agents to each other can be inferred via the Kaplan-Meier curves. In the present study we did not evaluate outcomes stratified by NSAID dose, given power limitations. Furthermore, the NSAID doses in our study were moderate, in accordance with approved labeling in the countries where the trial was conducted. In addition, data on erythrocyte sedimentation rate was not collected, and although baseline levels of C-reactive protein were reported, this variable was included post hoc and not adjusted for. The present study was not designed to evaluate outcomes on the basis of arthritis type (osteoarthritis or rheumatoid arthritis), though a separate analysis of PRECISION was recently published addressing this (34).

CONCLUSIONS

Among patients not taking aspirin, moderate-dose celecoxib is associated with a more favorable overall safety profile compared with naproxen or ibuprofen. Combination with aspirin attenuates the safety advantage of celecoxib, although celecoxib is still associated with fewer GI events than ibuprofen or naproxen and fewer renal events than ibuprofen. These results suggest that in many cases, celecoxib would be preferred to naproxen or ibuprofen, especially if the patient is not required to take aspirin.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: All NSAIDs increase cardiovascular, GI, and renal risk, but the risk profiles of the various NSAIDs differ and are modified by concomitant aspirin use. Celecoxib exhibits a more favorable overall safety profile than ibuprofen or naproxen and is not associated with increased cardiovascular risk, whether or not patients take aspirin concurrently.

TRANSLATIONAL OUTLOOK: The mechanisms by which aspirin and NSAIDs interact with respect to safety and efficacy are complex and probably not confined to COX specificity. Additional research is needed to elucidate these other contributing factors and delineate pharmacological strategies that maximize analgesic and cardiovascular benefit while minimizing risk.

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APPENDIX For a supplemental table and figures, please see the online version of this paper.